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LETTER TO THE EDITOR OF

PIGMENT CELL BULLETIN

MSH and its pigmentary role in mammals

Sir,

MSH stimulates melanosome dispersion in lower vertebrates and it is well recognized that in these animals it has an important role in the regulation of skin colour. Whether MSH has any physiological significance as a pigmentary hormone in mammals is, however, more debatable.

There is no doubt that MSH will stimulate coat darkening in a number of mammals through the mediation of cyclic AMP and the activation of tyrosinase, the key enzyme in the melanin pathway. We have shown that in the hair follicular melanocytes of the C3H-HeAvy mouse MSH stimulates the synthesis of tyrosinase and this accounts for the increase in tyrosinase activity that is necessary for eumelanin synthesis (Burchill et al, 1987). Whether MSH can also increase the catalytic activity of tyrosinase through a post-translational effect, as it does in melanoma cells (Fuller et al, 1987) is not yet known.

Stimulation of eumelanin synthesis is not exclusive to MSH since other activators of the cyclic AMP system, such as beta-agonists, are also effective (Burchill & Thody, 1986a). Dopamine agonists (D2), on the other hand, depress tyrosinase levels and decrease eumelanin production (Burchill et al, 1986; Burchill & Thody, 1986b). Interestingly, despite the low levels of tyrosinase phaeomelanin synthesis continues (Burchill et al, 1986; Burchill & Tody, 1986b), It appears that phaeomelanin synthesis, in contrast to that of eumelanin, is less dependent upon tyrosinase and this could explain why MSH fails to stimulate its production (Burchill et al, 1986). The synthesis of phaeomelanin is thought to be regulated by a factor related to the product of the agouti gene and it is possible that MSH, in inducing the eumelanin synthesis, may actually depress its expression (Tamate & Takeuchi, 1984), Whatever the mechanism of action it seems that MSH is only able to induce eumelanin synthesis in hair follicular melanocytes of mice that express the agouti gene. For instance, Geschwind et al (1972) showed that MSH has no effect on hair follicular melanocytes of non-agouti mice and we have since confirmed this. Whether the agouti gene regulates MSH action in hair follicular melanocytes of other species is not yet known.

The agouti gene certainly does not have the same importance in epidermal melanocytes (Tamate et al, 1986). Different regulatory

mechanisms may operate in epidermal melanocytes and apart from reports that MSH may enhance their differentiation in neonatal mice (Hirobe & Takeuchi, 1977), there is little evidence to suggest that epidermal melanocytes will respond to MSH (Nordlund et al, 1986; Seechurn & Thody, 1986). The same may also be true in man. Although high doses of MSH peptides may bring about skin darkening in man (Lerner & McGuire, 1964) human melanocytes in culture are unresponsive to MSH (Halaban et al, 1983; Friedmann & Gilchrest, 1987). We have also found no effects with either alpha-MSH or more potent analogues on tyrosinase in short term incubations of human skin. Furthermore, there seems to be no relationship between skin pigmentation and circulating levels of MSH peptides except when the levels are extremely high as in certain disorders of the pituitary adrenal axis (see Friedmann & Thody, 1986).

In conclusion it would appear that while MSH stimulates some pigment cells its pigmentary action is not as widespread as is commonly assumed. It may have a role in the regulation of coat colour in some species through its effect on hair follicular melanocytes but there is little evidence to suggest that is has any effect on epidermal melanocytes. In man UV is probably more important in the regulation of skin pigmentation, and any MSH-induced pigmentation is likely to be of pathological rather than physiological significance.

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University of Newcastle upon Tyne

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J Endocrinol 111:233-237.

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Alpha-melanocyte-stimulating hormone regulation of tyrosinase in Cloudman S-91 mouse melanoma cell cultures.
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Alpha-MSH and the differentiation of epidermal melanocytes in the C57BL mouse.
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Action of the and locus of mice in the response of phaeomelanic hair follicles to alpha-melanocyte stimulating hormone in vitro.
Science 224:1241-1242.

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J Exp Zool 238:235-240.

CURRENT LITERATURE IN

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ESPCR

PIGMENT CELL RESEARCH

1. MSH, OTHER HORMONES, DIFFERENTIATION

- Andersen AC, Pelletier G, Eberle AN, Leroux P, Jegou S, Vaudry H
Localization of melanin-concentrating hormone-like immunoreactivity in the brain and pituitary of the frog rana-ridibunda. Peptides (Fayetteville) 7:941-952, 1986.

- Castrucci AM
A teleost skin bioassay for melanotropic peptides. Gen Comp Endocrinol 66:374-380, 1987.
Abstract : A teleost (the eel, Synbranchus marmoratus) skin bioassay for melanotropic peptides and other agonists is described. Unlike previous teleost assays that generally monitor or observe individual melanophores, this objective assay utilizes large intact pieces of skin and quant. photoreflectance methods. Since melanosomes within most teleost melanophores are generally dispersed, the present assay provides a method for measuring the response of integumental melanophores to melanosome-aggregating agents such as a putative melanin-concentrating hormone (MCH). This bioassay is sensitive to MCH at a concentration as low as 10-12 M. Because of the magnitude of this lightening response, 4 point dose-response curves can be obtained. Skins lightened by MCH can be used for bioassay of melanotropins or other melanosome-dispersing agents such as .beta-adrenoceptor agonists. This bioassay is unique in providing a method for detg. the biol. activities of melanotropic peptides with opposing actions.

- Castrucci AM
Melanin concentrating hormone exhibits both MSH and MCH activities on individual melanophores. Life Sci 40:1845-1851, 1987.
Abstract : Asp-Thr-Met-Cys-Met-Val-Gly-Arg-Val-Tyr-Arg-Pro-Cys-Trp-Glu-Val (melanin-concg. hormone, MCH) and several fragment analogs (MCH1-14, MCH5-17, and MCH5-14) were synthesized and their biol. activities detd. in a very sensitivie fish (Synbranchus marmoratus) skin bioassay. The potency ranking an min. EDs of the peptides were MCH1-17 (10-12M) = MCH5-17 (10-12M) > MCH1-14, (10-11M) > MCH5-14 (2 times. 10-10M). The melanosome-aggregating activity of MCH could be completely reversed by a 100-fold higher concn. of alpha-MSH. MCH was self-antagonised in a dose-related manner by higher concns. of the peptide as was the activity of the MCH1-14 fragment analog. The MCH activities of the MCH5-17 and MCH5-14 analogs were not compromised by even the highest concns. of the peptides employed. The MSH-like activity of MCH appears to relate to the N-terminus of the hormone. Self-antagonism of MCH at high concns. appears to relate to the N-terminal tetrapeptide, which is respon-

sible for the intrinsic MSH-like activity of the hormone.

- Ciment G, Glimelius B, Nelson DM, Weston JA
Reversal of a developmental restriction in neural crest-derived cells of avian embryos by a phorbol ester drug. Dev Biol (US) 118:392-398, 1986.
Abstract : Neural crest cells and some of the cres-derived cells of dorsal root ganglia (DRG) of early avian embryos give rise to pigment cells when placed in culture. DRG from older embryos, however, fail to do so under comparable culture conditions. This age-dependent loss of melanogenic ability might be explained either by the death of a subpopulation of latent melanoblsts within early DRG, or the imposition of additional developmental restrictions in multipotent DRG cells. We show here that 12-O-tetradecanoyl-phorbol-13-acetate (TPA) causes some DRG cells to undergo pigmentation in cultures from older embryos, indicating that the loss of melanogenic ability in older embryos is not due to cell death. These pigment cells also display morphogenetic properties of normal melanocytes, including the ability to invade feather primordia. In addition to DRG, various other neural crest-derivatives contain cells similarly affected by TPA, including cells within symathetic ganglia and peripheral nerves. We suggest that TPA reverses the developmental restriction of melanogenic ability that is normally imposed on neural crest-derived cells that migrate to various sites in avian embryos where melanogenesis does not normally occur.

- Dexter TJ, Bennett DC
Differentiation apparently repressed by the nucleus. Rapidly-induced pigmentation of enucleated melanoma cells. Exp Cell Res 168:255-264, 1987.
Abstract : There is evidence for cytoplasmic control over gene expression in cell differentiation, but still very little is known of the intracellular mechanism, nuclear, cytoplasmic, or both, which actively initiates the differentiation of one cell type into another. Here the role of the cytoplasm was examined in the induction of differentiation of cultured mouse melanoma cells by melanocyte-stimulating hormone and alkaline medium. Intact cells were compared with cytoplasts, cells enucleated by centrifugation in the presence of cytochalasin D (CD). Surprisingly, early inductions of pigment (melanin) synthesis and of the principal melanin-synthesizing enzyme activity, tyrosinase, could be achieved in cytoplasts. Indeed, these early changes were slower in nucleated cells and were accelerated by the inhibitor of protein synthesis, cycloheximide. Thus the initial activation of tyrosinase and melanin synthesis - although not necessarily any other or later aspects of melanoma cell differentiation - is apparently controlled through a labile, transcription- and translation-dependent repression. To our knowledge this is a novel mechanism for the initiation of differentiation; its generality remains to be tested.

- Fellmann D, Bugnon C, Risold PY
Unrelated peptide immunoreactivities coexist in neurons of the rat lateral dorsal hypothalamus : human growth hormone-releasing factor 1-37-, salmon melanin-concentrating hormone- and alpha-melanotropin-like substances. Neurosci Lett 74:275-280, 1987.

- Ferroni EN, Castrucci AML
A sensitive in vitro toad skin bioassay for melanotropic peptides. Braz J Med Biol Res 20:213-220, 1987.

- Hadley ME, Zechel C, Wilkes BC, Castrucci AM, Visconti MA, Pozo-Alonso M, Hruby VJ
Differential structural requirements for the MSH and MCH activities of melanin concentrating hormone. Life Sci 40:1139-1145, 1987.
Abstract : H-Asp-Thr-Met-Arg-cyclo (Cys-Met-Val-Gly-Arg-Val-Tyr-Arg-Pro-Cys)-Trp-Glu-Val-OH, melanin concentrating hormone (MCH); exhibits both melanin granule concentrating and dispersing (MSH-like) activities. Fragment analogs were detd. In the frog (Rana pipiens) and lizard (Anolis carolinensis) skin bioassays, the 5-17 and 5-14 fragments of MCH were inactive (at concns. .ltoreq.10-5M) whereas the 1-14 sequence exhibited minimal (about 10%) MSH-like activity compared with MCH, which , as reported previously, was about 600 times less active than alpha-MSH. In the teleost (fish) skin bioassay, the MCH 5-17 analog was equipotent to MCH, whereas the 1-14 analog was 10-30 times and the cyclic N- and C-terminal truncated analog, MCH 5-14, was about 300 times less active than MCH. Apparently, the N-terminal sequence is particularly crit. to MSH-like activity in the tetrapod species studied, whereas other structural regions of MCH, particularly in the C-terminal, are more related to MCH activity in teleosts.

- Jones DB, Pedley RB, Ryaby JT
The effects of pulsating electromagnetic fields on differentiation and growth in cloudman S91 murine melanoma cells in vitro. J Bioelectr 5:145-170, 1986.

- Kawazoe I, Kawauchi H, Hirano T, Naito N
Characterization of melanin concentrating hormone in teleost hypothalamus. Gen Comp Endocrinol 65:423-431, 1987.
Abstract : Melanin concentrating hormone (MCH) is a heptadecapeptide isolated from chum salmon (Oncorhynchus keta) pituitaries. The peptide has been isolated from whole brain extract at a low yield of 1.2 micrograms/1300 brains. MCH activity in the hypothalamus was characterised by in vitro scal ebioassay and radioimmunoassay. Specificity of these assay systems was examined with neurotransmitters such as epinephrine, norepinephrine, and dopamine, hypothalamic hormones such as somatostatin, isotocin, Arg-vasotocin, oxytocin, and Arg-vasopressin, and salmon prolactin and his chymotryptic peptide or salmon PRL176-187. Among them only salmon PRL176-187 exhibited weak activities in both assays. The neurotransmitters were 10(4) to 10(5) times less potent than MCH in the bioassay. MCH concentrations in a pituitary and a hypothalamus were estimated as 5300 +/- 750 ng (ca. 106 micrograms/g) and 48 +/- 9.5 ng (ca. 1.6 micrograms/g), respectively, by radioimmunoassay. Lysyl endopeptidase digestion of the hypothalamic extract resulted in a significant increase of biological activity as well as of immunoreactivity. Gel filtration of the hypothalamic extract and subsequent enzymatic digestion revealed that the fractions at higher molecular weight were contributory to the increase in the activities.

- Kawazoe I, Kawauchi H, Hirano T, Naito N
Structure-activity relationships of melanin-concentrating hormone. Int J Pept Protein Res 29:714-721, 1987.
Abstract : Chem. and enzymatic modifications of melanin-concg. hormone (MCH) were conducted in order to deduce the structure-activity relation using an in vitro bioassay with fish scales, and a RIA using a specific antiserum to synthetic MCH. Micro-modification of MCH was employed with the natural peptide, and the modified form was purified by reverse-phase HPLC. MCH1-14 and nitrophenyl-sulfenyl-Trp15-MCH were equipotent to MCH. Redn. and carboxamidomethylation of MCh caused complete loss of biol. activity. Modification of the Tyr residue with tetranitromethane and Arg residues with 1,2-cyclohexadione reduced activity, whereas oxidn. with H2O2 caused only partial loss (10%) of activity. Evidently, the configuration of the S-S loop is essential for activity, and Arg and Tyr may play an important role in the biol. activity. In the RIA MCH1-14, MCH5-14, and carboxamidomethyl-Cys5,14-MCH showed no cross-reactivity, whereas MCH5-17 and other derivs. gave inhibition slopes parallel to the MCH std., suggesting that the antigenic determinant of the antiserum is located in the carboxy-terminal.

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Genetic controls over melanocytes differentiation : interaction of agouti-locus and albino-locus genetic defects. J Exp Zool 243:71-79, 1987.

- Levine N, Lemus-Wilson A, Wood SH, Abdel M
Stimulation of follicular melanogenesis in the mouse by topical and injected melanotropins. J Invest Dermatol 89:269-273, 1987.
Abstract : The effects of melanocyte-stimulating hormone (alpha-MSH) and related analogs on follicular melanogenesis in the mouse (C57BL/6JA gamma) were studied. (Nle4, D-Phe7)-alpha-MSH and the related fragment analogs Ac-(Nle4, D-Phe7)-alpha-MSH 4-11-NH2 and Ac-(Nle4, D-Phe7)-alpha-MSH 4-10-NH2; stimulated the conversion of pheomelanogenesis to eumelanogenesis when subcutaneously injected at concentrations 100 fold lower than the native hormone, alpha-MSH. In addition, the melanotropin analogs stimulated follicular eumelanogenesis when applied topically to the skin of mice. The melanotropins were transdermally delivered to the systemic circulation as evidenced by the fact that eumelanogenesis was stimulated in hair follicles in areas distant from the site of topical application. These results demonstrate that peptide hormone analogs can be transported across the skin. The unique actions of the melanotropin analogs may relate to the fact that these peptides are nonbiodegradable and thus exert prolonged actions on melanocytes. These compounds may prove important for studies on normal integumental melanogenesis and for the treatment of hypopigmentary disorders in humans.

- McLane J, Osber M, Pawelek JM
Phosphorylated isomers of L-dopa stimulate MSH binding capacity and responsiveness to MSH in cultured melanoma cells. Biochem Biophys Res Commun 145:719-725, 1987.
Abstract : The effects of dopa phosphates on receptors for MSH were examd. in cultures melanoma cells. Dopa phosphates caused a 3-fold

stimulation of MSH binding capacity by the cells which probably occurred through an increase in the no. of receptors for MSH with no apparent change in affinity of the receptors. The increased binding capacity for MSH was followed by increased cellular tyrosinase activity and melanogenesis. Thus, dopa phosphates and/or L-dopa can act as regulators of the MSH receptor system. The observations suggest a novel mechanism for regulation of hormonal responsiveness : hormonal signal amplification by a metabolite in the target pathway.

- Moriya R, Miyashita Y
Effects of cold on melanophore dispersion in isolated tail fin from amphibian tadpole. Zool Sci (Tokyo) 3:971, 1986.

- Naito N, Kawazoe I, Nakai Y, Kawauchi H, Hirano T
Coexistence of immunoreactivity for melanin-concentrating hormone and alpha-melanocyte-stimulating hormone in the hypothalamus of the rat. Neurosci Lett 70:81-85, 1986.
Abstract : Coexistence of immunoreactivity for melanin-concentrating hormone (MCH) and alpha-melanocyte stimulating hormone (alpha-MSH) within rat hypothalamic neurons has been examined by the unlabeled antibody enzyme method. Neurons exhibiting both MCH- and alpha-MSH-like immunoreactivities were found in the dorsolateral hypothalamus, whereas no MCH-like immunoreactive perikarya were seen in the arcuate nucleus, where some neurons were stained with alpha-MSH antiserum. There seem to be two distinct alpha-MSH-like immunoreactive neurons in the rat hypothalamus, one exhibiting coexistence with MCH-like immunoreactivity and the other not showing any cross-reaction with MCH antiserum.

- Nordlund JJ
In vitro modulation of proliferation and melanization of S91 melanoma cells by prostaglandins. Cancer Res. 47:3141-3146, 1987.
Abstract : The effects of prostaglandins (PGs) on the Cloudman S91 melanoma CCL 53.1 cell line indicate that melanogenesis and proliferation are regulated by sep. mechanisms that are not necessarily cAMP dependent. These cells responded to PGE1 and PGE2 in a dose-dependent manner, by an increase of tyrosinase activity and by inhibition of proliferation. PGA1 and PGD2 inhibited cellular proliferation and tyrosinase activity, whereas PGF2.alpha. had no effect after 24h of treatment. PGE1, but not PGE2 or PGD2, increased cellular cAMP levels after 30 min of treatment. Treatment with 10 mu.g PGE1/ml inhibited cellular proliferation after 4 h and enhanced tyrosinase activity afer 12 h. Tyrosinase stimulation by PGE1 required de novo transcription and translation. Actinomycin D, cycloheximide, and the tyrosinase inhibitor phenylthiocarbamide blocked tyrosinase activation but did not alter the inhibitory effect of PGE1 on proliferation. Dibutyryl cAMP and 3-isobutyl-1-methylxanthine augmented tyrosinase activation by PGE1 without enhancing the inhibitory action of PGE1 on cell growth. Neither blockage nor enhancement of the PGE1 effect on tyrosinase altered the PGE1-induced retardation of proliferation. These results are in marked contrast to the traditional concept that elevation of cAMP levels in melanoma cells necessarily results in stimulation of melanogenesis and inhibition of proliferation. The data presented

propose independent and possibly alternative pathways for the regulation of these two cellular events.

2. MORPHOLOGY OF PIGMENT CELLS AND PIGMENTARY DISORDERS

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Pigmented actinic keratoses. Hautarzt 37:676-678, 1986.

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Large melanosome complexes in the human gingival epithelium. J Peridont Res 22:108-113, 1987.

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Congenital nystagmus among the red-skins of the Highlands of Papua New Guinea. Br J Ophthalmol 64:375-380, 1980.

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Immunohistochemical demonstration of S100 protein in melanin-producing tumors after bleaching for melanin. Rinsho Byori 35:316-318, 1987.

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Pigmented dermatofibrosarcoma protuberans. Report of two cases as a variant of dermatofibrosarcoma protuberans with partial neural differentiation. Am J Dermtopathol (US) 9:18-25, 1987.

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Thioredoxin reductase. Role in free radical reduction in different hypopigmentation disorders. Arch Dermatol (US) 123:615-619, 1987.

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Melanin-pigment in complex odontoma. Int J Oral Maxillofac Surg 16:222-226, 1987.

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Mast cells containing melanin granules in sublingual keratosis. J Oral Pathol 16:108-111, 1987.

- Wright CG, Lee DH
Pigmented epithelial cells of the membranous saccular wall of the chinchilla. Acta Otolaryngol 102:438-449, 1986.

3. MELANIN CHEMISTRY, BIOLOGY, HISTOCHEMISTRY AND OTHER PIGMENTS

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Fox colors in relation to colors in mice and sheep. J Hered 78:235-237, 1987

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Interference of melanin in protein determination. Anal Biochem 159:249-252, 1986.

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Test for linkage between the eumelanin restrictor (Db) and the eumelanin extension (MI) genes in the domestic fowl. Br Poult Sci 28:69-73, 1987.

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Relative positions of the loci of the peacomb (P), eumelanin restrictor (Db), eumelanin extension (Ml) and plumage pattern (Pg) genes of the domestic fowl. Br Poult Sci 28:347-350, 1987.

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Oxidation of dopa in the skin of black and albino mice. Acta Derm Venereol 66:369-374, 1986.

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ESCA analysis of melanin compounds. Polym Prepr (Am Chem Soc, Div Polym Chem) 28:196-197, 1987.
Abstract : Natural melanin and various synthetic melanin and melanochrome compds. were analyzed by ESCA. By using the chem. stds., the binding energies of the various functional groups believed to be in the melanin compds. can be assigned. The chem. stds. were also used to show that the ESCA mass ratios compared to the theor. elemental ratios. In the proposed eumelanogenesis scheme, differences can be detected in the starting material, melanochromes, melanins, and the melanin-free-acids. Finally, ESCA proves to be a useful technique in analyzing melanin compds.

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Photooxidation of 5,6-dihydroxy-1-methylindole. Tetrahedron 43:431-434, 1987.
Abstract : Photooxidn. of the title compd. (I) in MeOH with Pyrex-filtered UV light gave a complex mixt. of fluorescent compds. The major isomer. isolated as the acetoxy deriv. , was 2,4'-biindolyl deriv. II. Two triacetoxyindoles, two pentaacetoxy dimers, and a diacetoxyoxindole were also isolated from the photolysis soln. The relevance to the photochem. processes fro light-induced melanin formation and assocd. processes is discussed. For diagram(s), see printed CA issue.

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Does melanin do more than protect from light ? Neurosci Res (Shannon, Irel.) S75-S86, 1987.

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The melanin pigments of moles. Priroda (Sofia) 36:62-67, 1987.

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Quenching of singlet molecular oxygen by the screening pigments melanin and ommochrome. Biofizika 32:685-686, 1987.

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Rapid bleach for melanin. Stain Technol 61:239-242, 1986.

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Spin-label assay for aqueous solutions of transition-metal ions with application to melanin. J Magn Reson 71:313-321, 1987.

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Fluorescence of melanin-dependence upon excitation wavelength and concentration. Photochem. Photobiol. 45:595-600, 1987.
Abstract : An introduction to the fundamental characteristics of synthetic melanin fluorescence is presented. The particular difficulties assocd. with the detection of redn. of the relatively weak signal are deiscussed and a technique is described for correcting the fluorescence spectra for attenuation of the excitation and emission beams. Spectra are reported for the excitation wavelength range 340-400 nm and an emission range of 360-560 nm. The concn. dependence of the cor. fluorescence signal is examd. and shown to be linear. The variation of the fluorescence spectra with excitation wavelength suggests a 2 component fluorescence, for the wavelenght range studied. The presence of an isosbestic point in the spectra is used to identify the fluorophores as components of a reaction equil. The possible relationship of this equil. to that assocd. with the melanin photo ESR is discussed.

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Preparation of N,N-dialkyl-p-hydroxycinnamamides as melanin inhibitors. 1987.
Abstract : The title compds. (I; R1, R2 = alkyl), useful as melanin inhibitors, are prepd. Aq. 40% Me2NH (0.25 mol) was added to a soln. of 0.12 mol 4-AcOC6H4CH:CHCOCl in CH2C12 at 15-20 degree, and the mixt. was stirred at room temp., refluxed, and hydrolyzed with 12% HCl to give 81% I (R1 = R2 =Me), application of which gave a much reduced pigment deposit on guinea pig skin after exposure to UV radiation. For diagram(s), see printed CA Issue.

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Effect of melanin on the free-radical states of gamma-irradiated proteins and lipids. Radiobiologiia (USSR) 27:8-11, 1987.
Abstract : It was shown that the concentration of paramagnetic centres of dihydroxyphenylalanine-melanin increased after gamma-irradiation (60Co) both at room temperature (an irreversible increase) and at 77K (a reversible increase). The accumulation of paramagnetic centres in gamma-irradiated albumin at room temperature was found to slow down appreciably in the presence of melanin. This effect is thought to be associated with the antiradical activity of the pigment.

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Inhibitors of melanogenesis. Fragrance J 15:42-48, 1987.
Abstract : A review with 31 refs. discussing melanogenesis inhibi-

tors (e.g. ascorbic acid phosphate, kojic acid, placenta ext., tocopherols and plant ext.).

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Melanin affinity of xenobiotics. Upsala J Med Sci 91:283-288, 1986.

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Melanocytes of the semilunar planes of the internal ear in the guinea pig. Histochemical and ultrastructural research. Arch Ital Anat Embriol 91:43-61, 1986.

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Abstract : Significant levels of intracellular catecholamines were found in a human melanoma cell line and were enhanced by increasing the extracellular tyrosine concns. Intracellular dopa, 5-S-cysteinyldopa, tyrosinase, and melanin also rose under these conditions. 5-HT was synthesized by the melanoma cells, but further study was hindered by the high level of 5-HT in fetal calf serum. A 5-HT uptake antagonist, DU 24565 (6-nitroquipazine), was employed as an alternative method for studying 5-HT action. This compd., which in contrast to tunicamycin had no inhibitory effects on cell proliferation or tyrosinase activity, strongly inhibited melanization and decreased the levels off dopa, 5-S-cysteinyldopa, dopamine, noradrenaline, adrenaline, and 3,4-dihydroxyphenylacetic acid. DU 24565 had little effect on 5-HT or tyrosine accumulation in these cells, but suppressed the uptake of extracellular dopa. The results show that human melanoma cells synthesize a wide range of biogenic amines in culture and suggest a new approach to regulating intracellular levels of dopa and a variety of dopa products.

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Abstract : As models of possible intermediates in the melanogenesis of 3,4-dihydroxyphenylalanine (DOPA), 1,2-benzoquinones I (R = CH:CHCO2H, (CH2)2CO2H, (CH2)2CO2Me, CH2CH(NH2)CO2H, etc) were prepd. by ceric ammonium nitrate oxidn. of the corresponding catechols. Trapping of I with indole II gave propellanes III (same R's). For diagram(s) , see printed CA Issue.

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Abstract : The title carboxylic acid (I), a structural unit in the biosynthesis of melanin, underwent autoxidn. in the presence of CoSO4. Redn. of the reaction mixt. with Na2S2O4 followed by esterification with MeOH-HCl and acylation gave biindolyl II as the major component. It was also prepd. by NaIO4 oxidn. of DOPA-Me ester III in the presence of Co+2 followed by similar derivatization. Coupling of phenoxyl radicals is suggested for the conversion of I to melanin. For diagram(s), see printed CA Issue.

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Abstract : In vitro expts. are reported showing that a no. of transition metal ions exert a profound influence on both the kinetics and chem. course of the rearrangement of dopachrome (I), a key step in the biosynthesis of melanins. HPLC anal. shows tat Cu2+, Ni2+, and Co2+ are particularly effective in inducing the nondecarboxylative rearrangement of I at physiol. pH values, leading mainly to 5,6-dihydroxyindole-2-carboxylic acid, whereas in the absence of metal ions the reactin proceeds with concomitant loss of CO2 to give almost exclusively 5,6-dihydroxyindole. Kinetic expts. provide evidence that the rate of the metal-promoted rearrangement is 1st-order with respect to both aminochrome and metal concn. and decreases in the presence of increasing concns. of EDTA, consistent with a mechanism involving a direct 1:1 I-metal ion interaction in the transition state. The results provide a new entry into the regulatory mechanisms involved in the biosynthesis of melanins. For diagram(s), see printed CA Issue.

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Analysis of the ESR spectrum of synthetic dopa melanin. Biochim Biophys Acta 884:510-516, 1986.
Abstract : The 35 GHz ESR spectrum of frozen aqueous suspensions of synthetic melanin from autoxidation of dopa is asymmetric in the pH range 3-12. This asymmetry increases with increasing pH. A detailed computer analysis of second-derivative spectra suggests that the asymmetry is a result of two factors : approximately axial anisotropy of the g-tensor of the radical species; superposition of ESR spectra arising from a total of four radical species. The relative amounts of these individual spectra vary in a pH-dependent manner. Anisotropy of spectra varies with pH, probably due to pH-induced changes in the delocalization of the unpaired electrons. Thus the species present at high pH are suggested to be relatively localized radical anions, while the species detected at low pH are suggested to be protonated forms of the high pH species in which the unpaired electron is more extensively delocalized.

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A comparison of the melanocyte response to narrow band UVA and UVB exposure in vivo. J Invest Dermatol 88:774-779, 1987.

Abstract : The visible cutaneous pigmentary response to UVA is immediate and, following sufficient exposure, may persist, whereas UVB-induced pigmentation appears after a delay of several days. The in vivo response of human melanocytes was compared to single and multiple exposures of narrow ban UVA and UVB irradn. which produced visibly equal increases in pigmentation. Using a Xe-Hg source matched to a monochromator, human volunteers were exposed to 304- and 365-nm radiation. Biopsies were performed 1, 7, and 14 days after irradn. For each biopsy, the no. of melanocytes per square millimeter of epidermis was detd. using L-dopa- and tyrosine-incubated split epidermal prepns. Vertical sections were also examd. At days 7 and 14, after both 304 and 365-nm radiation, melanocytes were more intensely dopa-pos. than in unirradiated controls, and demonstrated enlarged perikarya and a greater no. of enlarged dendrites. Following both 304- and 365-nm irradn., the no. of dopa-pos. melanocytes was increased at days 7 and 14 by 44 and 58%, resp. Tyrosine positivity, an indicator of enhanced tyrosinase activity and increased melanin formation, was absent in controls and at day 1, and became pos. in all but 1 sample at day 7 and day 14. Therefore, 1 day after UVA exposure, visible pigmentation but not tyrosinase activity was increased. At day 7, the no. of tyrosine-pos. melanocytes approx. equaled the no. of dopa-pos. melanocytes. Although UVA and UVB induce different pigmentary responses, their effects on melanocyte no. and function were undistinguishable.

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Relationship between melanin content and superoxide dismutase (SOD) activity in the liver of various species of animals. Cell Biochem Funct 5:123-128, 1987.
Abstract : The scavenger effect of melanin and of superoxide dismutase (SOD) activity on superoxide anion has been shown. In this work we show the relationship between melanin content and SOD activity in livers containing different quantities of melain which were taken from various species of animals. The mitochondrial SOD activity disappears when the melanin content in the liver is very high; moreover it increases, in the liver of various species of animals examined, proportionally to the decrease of melanin content. No significant variation of the SOD activity localized in the soluble fraction has been detected when related to the melanin content. We think that in the pigmented liver the antioxidant activity of the melanin could mimic part of the function of SOD. The loss of Mn SOD activity culd be mediated by a low intracellular level of superoxide anion due to the scavenger effect of melanin on superoxide anion; in fact, it is well known that the biosynthesis of Mn SOD is induced by intracellular levels of superoxide anion.

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Electron spin resonance spectrometric study of the melanins in the wool of some North European sheep in relation to their color inheritance. J Hered 78:120-122, 1987.

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Melanin-related metabolites as markers of the skin pigmentary system. J Invest Dermatol 89:78-81, 1987.
Abstract : The urinary excretion of 3,4-dihydroxyphenylalanine (dopa), 5-S-cysteinyldopa (5-S-CD), and 2 indolic compds., namely 5-hydroxy-6-methoxyindole and 5-hydroxy-6-methoxyindole-2-carboxylic acid (5H6MI2C) were measured in urine samples of 4 groups of people with different contents of cutaneous melanin : (a) Asian group; (b) white group, and 2 groups and whites (c) 1 with vitiligo and (d) 1 with tyrosinase-neg. oculocutaneous albinism. Comparison of the melanin-related metabolites excreted in urine of people with different capacities for melanin biosynthesis indicates that, of all measured substances, 5H6MI2C is the best urinary marker of melanin formatio in the skin pigmentary system.

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Chemical- and photo-bleaching of brown and red hair. J Soc Cosmet Chem 38:179-191, 1987.
Abstract : The color of mammalian hair is mainly due to the presence of melanin pigments that are introduced into the keratinized cytoplasmic protein during the process of fiber formation. The melanins fall into 2 chem. distinct classes : eumelanin, derived from enzyme oxidn. of DOPA, and pheomelanin, formed from 5-S-cysteinyl DOPA. The eumelanin is found in black and brown hair, while pheomelanin is the red hair colorant. The changes in hair color that are attendant upon bleaching with H2O2 or upon exposure to sunlight were studied by using reflectance measurements. Pheomelanin is more resistant than eumelanin to chem. or photo-degrdn., a finding supported by a parallel series of in vitro expts. with the isolated pigments. Shifts in the hue of bleached tresses were obsd., and an explanation of these in terms of changes in phys. and spectral characteristics of the melanin pigment is proposed.

4. NEUROMELANINS

- D'Amato RJ, Alexander GM, Schwartzman RJ, Kitt CA, Price DL, Snyder SH
Evidence for neuromelanin involvement in MPTP-induced neurotoxicity. Nature (London) 327:324-326, 1987.
Abstract : Pretreatment of monkeys (Macaca fascicularis) with chloroquine partially protected the animals from the biochem. and

neurolog. effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MTPT), a compd. that induces many symptoms of Parkinson's disease. Since chloroquine and a MTPT metabolite are competitive binders to melanin, chloroquine may inhibit the melanin binding, neural uptake, and gradual releases of the metabolite (which would normally destroy dopaminergic neurons). Thus, neuromelanin is apparently involved in mediation of the neurotoxicity of MTPT.

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Distribution of melanocytes and chemical analysis of melanin in labyrinth. Pract Otol Kyoto 0(sup.8):1-8, 1986.

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5. PHOTOBIOLOGY AND PHOTOCHEMISTRY

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Biochemical and technical aspects of solar protection. Prod Chim Aerosol Sel 28:35-44, 1987.

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Matrix effects in secondary ion mass spectrometric analysis of biological tissue. Scanning Electron Microsc 1986:1277-1290, 1986.

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Long-term actinic damage in sun-exposed vitiligo and normally pigmented skin. Dermatologica 174:266-271, 1987.
Abstract : Vitiligo provides a model system for studying chronic actinic damage in skin devoid of melanin pigments and thereby permits assessment of their photoprotective function. Our study comprised 23 patients with a mean age of 67 years having stable, long-lasting vitiligo on light-exposed body regions. The vitiliginous and normally pigmented, light-exposed skin was examined clinically for manifestations of chronic actinic damage. In 11 patietns skin biopsies were obtained from vitiliginous and adjacent pigmented skin for qualitative and quantitative histological comparison. Our study did not reveal evidence for a significant increase of chronic actinic damage in skin devoid of melanin pigments. These results are in agreement with the rareness of reported skin cancer in vitiligo.

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Sunburn cell : factors involved in its formation. Phtochem Photobiol 45:683-690, 1987.

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Abstract : When the melanin-producing genes in the human skin are in full working order the melanin production is far greater than it needs to be under present day conditions. The likely correct

postulate for explaining this apparent anomaly of an uncaused biological property is that there have been times in the past when the situations was markedly different. The requirement is for a greater penetration of the Earth's atmosphere by serious sunburn radiation shortward of 3000 A. This requirement demands an absorption at high altitudes of the solar radiation at proportional 2000 A which is at present responsible for the formation of the ozone layer. A distribution of small particles with total mass proportional 3 x 1014 grams at atmospheric altitudes above 30 Km, the small particles having refractive index proportional 1.5-0.1i at lambda approx. = 2000 A, meets the necessary conditions (orig.).

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Development of biomimetic sunscreens and their applications. Fragrance J 15:59-63, 1987.

- Koch WH, Chedekel MR
Photochemistry and photobiology of melanogenic metabolites : formation of free radicals. Photochem Photobiol 46:229-238, 1987.

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Photogeneration of free radicals from eumelanogenic intermediates and metabolites. Biochim Biophys Acta 924:458-466, 1987.
Abstract : It has recently been demonstrated that cysteinyldopas, pheomelanogenic precursors, and excreted eumelanogenic metabolites are photolabile and initiate DNA damage in vitro. In this study, the photochem. investigations have been extended to eumelanogenic indole intermediates and metabolites. Continous-wave photolysis (300nm) of 5,6-dihydroxyindole (DHI), 5,6-dihydroxyindole-2-carboxylic acid (DHICA), or its 5-methoxylated metabolite (HMICA) with biol. relevant UV radiation (i.e., wavelenghts > 300 nm) resulted in rapid destruction of starting material. Using ESR spin-trapping techniques, the initial prodn. of free radical species was obsd. and prolonged photolysis resulted in the formation of polymeric photoproducts. Radicals were trapped by the nitrone spin trap DMPO and characterized by their ESR spectra as hydrated electrons and H atoms. Expts. further demonstrated that while DHI photoionizes, the 2 indole-2-carboxylic acid derivs. do not ionize appreciably upon irradn.; rather, hydrolysis of X-H bonds appears to be a significant photochem. pathway. The potential photobiol. significance of melanogenic indole intermediates is discussed.

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Nonlinear optical and electro-optical properties of biopolymers. Springer Proc Phys 18:110-130, 1987.
Abstract : Photodiffractive effects of a polyethylenepolyamine contg. chromophoric side groups were discussed and compared with those of melanin. Nonlinear optical properties of org. compds. and biopolymers were also reviewed.

- Land EJ, Thompson A, Truscotte TG, Subbarao KV, Chedekel MR
Photochemistry of melanin precursors dopa 5-S cysteinyldopa and 2 5-S' dicysteinyldopa. Photochem Photobiol 44:697-702, 1986.
Abstract : The photochemistries of the melanin precursors dopa, 5-S-cysteinyldopa (5-SCD) and 2,5-S,S'-dicysteinyldopa (2,5-SCD) were

investigated by 265-nm laser flash photolysis. The quantum yield of hydrated electron following flash photolysis of dopa (9.1%) was half the yield of dopasemiquinone (19.6%), implying that dopasemiquinone is formed via two primary photochemical mechanisms : photonisation (giving e-aq) or photohomolysis (giving H'). Dopasemiquinone rapidly disproportionates to form dopaquinone and re-form dopa. Dopaquinone in turn decays via a base-catalysed unimolecular cyclisation eventually to form dopachrome. Assignment of the transient species was confirmed by previous pulse radiolysiss studies of the one-electron oxidation of dopa. In contrast, flash photolysis of the cysteinyldopas, 5-SCD and 2,5-SCD results in lower photoionisation quantum yields and the production of initial transient species whose absorption spectra were markedly different from their semiquinone absorption spectra previously determined pulse radiolytically. These observations indicate that the primary cysteinyldopa photochemical species is not such a semiquinone, but rather results from S-CH2 bond photohomolysis. Absorption spectra and rate constants for the formation and decay of various transient species are reported.

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Vitiligo, still an enigma ! (editorial). Dermatologica 174:261-265, 1987.

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Principles of photoprotection in sunburn and suntanning, and topical and systemic photoprotection in health and diseases. J Dermatol Surg Oncol 11:575-579, 1985.

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Photolysis of pheomelanin precursors an Esr-Spin trapping study. Photochem Photobiol 44:689-696, 1986.

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Melanosomes are a primary target of Q-switched ruby laser irradiation in guinea pig skin. J Invest Dermatol 89:281-186, 1987.
Abstract : The specific targeting of melanosomes may allow for laser therapy of pigmented cutaneous lesions. The mechanism of selective destruction of pigmented cells by various lasers, however, has not been fully clarified. Black, brown, and albino guinea pigs were exposed to optical pulses at various radiant exposure doses from a Q-switched, 40 nsec, 694 nm ruby laser. Biopsies were analyzed by light and electron microscopy (EM). Albino animals failed to develop clinical or microscopic evidence of cutaneous injury after irradiation. In both black and brown animals, the clinical threshold for gross change was 0.4 J/cm², which produced an ash-white spot. By light microscopy, alterations appeared at 0.3 J/cm² and included separation at the dermoepidermal junction, and the formation of vacuolated epidermal cells with a peripheral cytoplasmic condensation of pigment. By EM, enlarged melanosomes with a central lucent zone were observed within affected epidermal cells at 0.3 J/cm². At 0.8 and 1.2 J/cm², individual melanosomes were more intensely damaged and disruption of melanosomes deep in the hair papillae was observed. Dermal-epidermal

blisters were formed precisely at the lamina lucida, leaving basal cell membranes and hemidesmosomes intact. Possible mechanisms for melanosomal injury are discussed. These observations show that the effects of the Q-switched ruby laser are melanin-specific and melanin-dependent, and may be useful in the selective destruction of pigmented as well as superficial cutaneous lesions.

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Effects of melanin-induced free radicals on the isolated rat peritoneal mast cells. J Invest Dermatol 86:303-307, 1986.
Abstract : Pheomelanin from human red hair (RHM) produces considerably more cellular damage in Ehrlich ascites carcinoma cells when subjected to radiations of wavelenght 320-700 nm than eumelanin from black hair (BHNM). Irradiation of RHM generated large amounts of superoxide while BHM did not produce detectable amounts of superoxide. The present investigations describe the effects of irradiation of mast cells in the presence of various natural and synthetic melanins. Irradiation of mast cells in the presence of RHM and red hair melanoprotein released large amounts of histamine while BHM and synthetic melanins prepared from dopa, cysteinyldopa, or a mixture of dopa and cyteinyldopa did not release histamine. The release of histamine at lower concentrations of RHM was not accompanied by the release of 51Cr from chromium-loaded cells, suggesting that this release was of noncytotoxic nature. On the other hand, the release of histamine at higher concentrations of RHM was due to cell lysis since both histamine and cytoplasmic marker 51Cr were released to the same extent. The release evoked by large concentration RHM was not inhibited by superoxide dismutase or catalase. This suggests that the cell lysis under these conditions was not due to H2O2 or O-2. The finding that mast cells release histamine when irradiated in the presence of RHM suggests that the immediate and late-phase reactions seen in sunburn may in part be due to the release of mediators from these cells.

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UVA induced darkening of lower epidermal cells as an in vitro system of immediate pigment darkening (IPD) and mechanisms of IPD. J Dermatol 13:101-107, 1986.

- Tomita Y, Fukushima M, Tagami H
Stimulation of melanogenesis by cholecalciferol in cultured human melanocytes : a possible mechanism underlying pigmentation after ultraviolet irradiation. Tohoku J Exp Med 149:451-452, 1986.

- Tong AK, Tan OT, Boll J, Parrish JA, Murphy GF
Ultrastructure : effects of melanin pigments on target specificity using a pulsed dye lase (577 nm). J Invest Dermatol 88:747-752, 1987.

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Sensitivity of mouse SKH HR-2 to UV radiation melanocyte inactivation. J Invest Dermatol 88:266-270, 1987.
Abstract : The hairless mouse, Skh:HR-2, was exposed to doses of ultraviolet (UV) radiation known to induce skin pigmentation. Three parameters associated with perturbations in skin pigmentation

were monitored following UV exposure. These include spectroscopy (Skin darkness), histology (melanocyte density) and biochemistry (melanin). Within 90 min of UV exposure, the skin became lighter. This was associated with a reduction of quantifiable melanin and the inactivation of epidermal melanocytes.

6. MELANOMA

- Agui T, Bryant G, Kebadian JW, Larson S, Saavedra JM, Shigematsu K, Yamamoto T, Yokoyama K
125I-iodinated benzazepines bind to melanin : implications for the noninvasive localization of pigmented melanomas. Int J Rad Appl Instrum 14:133-141, 1987.
Abstract : Both the 5-R and the 5-S enantiomers of (125I)2,3,4,5-tetrahydro-8-iodo-3-methyl-5-phenyl-1H-3-benzazepin-7-ol bind to melanin. The interaction between the 5-R enantiomer and melanin permits visualization of melanomas in mice with a noninvasive imaging procedure. Two lines of evidence suggest that the interaction between iodinated ligands and melanin is not related to the D-1 dopamine receptor, a known target for the 5-R enantiomer : first, melanin binds both enantiomers of the 125I-iodinated benzazepine while the D-1 receptor binds only the 5-R enantiomer; second, the melanin binding site displays only a 5-fold difference in affinity towards the R- and S-enantiomers of SCH 23390 while the D-1 receptor displays a 100-fold difference in affinity towards these two molecules. Because both enantiomers of the iodinated benzazepine bind to a human pigmented melanoma, we propose that such compounds may be of use in the diagnosis of pigmented melanoma : in addition, we discuss the possible application of these molecules as a supplement to existing technology for the localization of pigmented melanomas.

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Glucocorticoid effect on melphalan cytotoxicity, cell-cycle position, cell size, and (3H)uridine incorporation in one of three human melanoma cell lines. Cancer Res 47:4814-4820, 1987.
Abstract : Three human melanoma cell lines of known content of specific glucocorticoid-binding sites were studied for colony formation after a microM dose of glucocorticoid combined with melphalan. In one of the three cell lines, M-5A, subcloned from M-5 (formerly designated RPMI 8322), the effect of combined treatment was markedly increased compared to that of melphalan even if the glucocorticoid was applied for 1 h only, 10 h before the melphalan. Semilogarithmic dose-effect plots for a reduction of final plating efficiency by glucocorticoid were curvilinear, according to a receptor-mediated process. The effects of glucocorticoid, melphalan, and their combination were linearized by bilogarithmic median-effect plotting which allowed the quantitation of a synergism which was more marked in case of glucocorticoid pretreatment, for 1 or 24 h, than on simultaneous exposure. According to sequential DNA per cell cytophotometry, melphalan abolished in M-5A a glucocorticoid-induced arrest in the G1 phase of the cell cycle. The cytotoxic synergism correlated with an apparent stimulation by glucocorticoid

of the rate of acid-insoluble incorporation of (3H)uridine and (C14)leucine and an increase in cell size and protein content in M-5A cells but not in the other two cell lines. The way in which glucocorticoids induce an enhanced susceptibility to melphalan is not clear. Our results appear compatible with a hypothesis that chromatin in a transcriptionally activated state is more vulnerable to cytotoxic attack by an alkylating agent than under average conditions.

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Regression of cutaneous metastatic melanoma by intralesional injection with human monoclonal antibody to ganglioside GD2. Proc Natl Acad Sci USA 83:8694-8698, 1986.
Abstract : In this study we used human monoclonal antibody (Hu-mAB) L72 as an intratumoral injection of cutaneous metastasis of melanoma to study its anti-tumor effects in human patients. Hu-mAB L72 was developed by transforming peripheral blood lymphocytes from a melanoma patient in vitro with the Epstein-Barr virus, forming a human lymphoblastoid cell line that produces 2-5 micrograms of IgM per ml. This IgM Hu-mAB was shown to react specifically with ganglioside GD2 and have a strong cytotoxic effect on human melanoma cells in the presence of complement. Patients with cutaneous metastatic melanoma were given intralesional injections on a daily or weekly injection schedule. Regression was seen in all tumors except in those of two patients whose tumors were shown to have low antigenicity. Histopathological data showed tumor degeneration, fibrosis, free melanin, and some degree of lymphocyte or macrophage infiltration. One patient with melanoma satellitosis treated with Hu-mAB showed complete regression with no sign of recurrence 20 months after the initial treatment. With the exception of mild erythema, no side effects were observed in any patient.

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Selective cytotoxicity of 4-S-cysteaminylphenol on follicular melanocytes of the black mouse : rational basis for its application to melanoma chemotherapy. Cancer Res. 47:3278-3284, 1987.
Abstract : 4-S-cysteaminylphenol (4-S-CAP) was previously shown to cause a significant inhibition of in vivo melanoma growth. To clarify the mechanism of this antimelanoma effect, the cellular and subcellular changes of folicular melanocytes after s.c. administration of 4-S-CAP on the lumbar areas of black and albino mice were studied. 4-S-CAP produced a prompt, selective swelling and lysis of melanocytes, resulting eventually in the necrosis of melanocytes and the depigmentatin of black hair follicles. None of the degenerative changes were seen in melanocytes and keratinocytes of control albino follicles. Comparison of melanocytes in black and albino follicles revealed that melanin synthesis is highly active in the melanocytes of black follicles while melanin and tyrosinase synthesis is not seen in the melanocytes of albino follicles. Apparently, the selective melanocytotoxicity of 4-S-CAP is manifested by lysis and necrosis of cells which are actively engaged in melanin synthesis. 4-S-CAP appears to provide a new modality for rational chemotherapy of malignant melanoma.

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Detection of melanin-containing matter with benzazepines. 1986.
Abstract : A method for detecting melanin-contg. matter utilizes an enantiomer of 2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepin-7-ol (BZZ) which binds to melanin. BZZ can be labeled with 125I or contain a Cl at position 8. Following i.v. administration of 10 .mu.Ci (125I)BZZ, radioactivity rapidly accumulated in the eyes of the pigmented C57BL/6 mouse but not in the eyes of the albino Swiss Webster mouse. In vitro autoradiog. confirmed that the pigment epithelium of the retina was the ocular structure accumulating 125I. Within 45 min. after i.v. injection of 10 .mu.Ci (125I)BZZ into an albino mouse carrying B16 melanoma, the concn. of radiolabel accumulated within the melanoma was 19-fold greater than that within the nonpigmented eye. Comparison of the binding affinities of BZZ to D1 dopamine receptors and melanin showed that the D1 receptor had a 100-fold higher affinity for the r-enantiomer of BZZ than for the S-enantiomer. In contrast, melanin was less stereoselective, with only a 5.1-fold difference between the enantiomers. Thus, the S-enantiomer was preferred for localization of melanomas.

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Generalized melanosis of macro- and microphages in metastasizing melanoma. Hautarzt 38:232-234, 1987.

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Biochemical markers of malignant melanoma. Neoplasma 34:77-84, 1987.
Abstract : From the results of a study with human patients with primary and/or metastatic cutaneous melanoma and healthy persons, urinary excretion of Thormaehlen-pos. melanogens and the dopa oxidase activity of serum tyrosinase proved to be specific markers for melanoma growth. The concn. of serum sialic acids proved to be valuable in following the progress of the disease. Urinary excretion of Zn could not be used to monitor melanoma patients because the values were small.

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Accumulation of chlorpromazine and thiouracil by human melanoma cells in culture. Aust J Exp Biol Med Sci 64:517-526, 1986.
Abstract : The uptake (total radioactivity in intact cells) and incorporation (radioactivity bound to acid-precipitable material) of 14C(chlorpromazine) (CPZ) and 14C(thiouracil) (TU) were studied in human fibroblast and tumor cell lines. In contrast to previous studies using rodent melanomas in vivo, the melanoma lines, including lines with high tyrosinase and melanin contents, did not take up more CPZ and TU than nonmelanoma cells (fibroblasts, HeLa cells). Incorporation of CPZ was also broadly similar in all cell types studied. TU was selectively incorporated into the melanoma line having a high tyrosinase and melanin content but not into lines with high tyrosinase activity and low melanin content. While supporting the possibility of selective therapy for heavily-pigmented melanomas using radiolabeled TU derivs., these results sug-

gest that the action of potentally melanoma-affined compds. should be further evaluated in human cells. Unlabeled CPZ or TU was not selectively toxic to melanoma cells. Unexpectedly, methylation-sensitive tumor cells (Mer- phenotype) were highly resistant to TU, thus providing a new exptl. tool for understanding the genesis of this phenotype in vivo.

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Melanosis and colonic neoplasms. Lyon Chir 82:318-319, 1986.

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Monoclonal antibody specific for a pigmentation-associated antigen of melanocytes and melanoma cells. Eur Pat Appl EP 208902 A2, 1987.

7. TYROSINE AND OTHER ENZYMES

- Burchill SA, Thody AJ
Dopaminergic inhibition of tyrosinase activity in hair follicular melanocytes of the mouse. J Endocrinol 111:233-237, 1986.
Abstract : Bromocriptine, a dopamine agonist that blocks the secretion of MSH, inhibits melanogenesis in the hair follicular melanocytes of pubertal C3H-HeAvy mice. However, since this effect cannot be explained by a reduction in circulating alpha-MSH, we have examined the possibility that dopaminergic mechanisms may have a direct inhibitory effect on these melanocytes. Bromocriptine devreased tyrosinase activity in skin explants from 30- to 35-day-old mice that were growing dark hair. This decrease in tyrosinase activity was blocked by dopamine receptor antagonists, haloperidol or spiperone. The specific D2 agonist LY 171555 also inhibited tyrosinase activity in the skin explants in a dose-related manner and the effect was blocked by sulpiride, a D2-receptor antagonist. Neither bromocriptine nor LY 171555 had any effect on tyrosinase activity in skin explants taken fromadult mice that were growing yellow hair. The D1-receptor agonist SKF 38393 had no effect on tyrosinase activity in skin explants from either group of mice. The present results support the idea that dopamine D2-receptor agonists have a direct inhibitory effect upon tyrosinase activity of hair follicular melanocytes of the C3H-HeAvy mouse. However, this effect was confined to periods of dark hair growth when the melanocytes produce eumelanin. The D2 agonists were ineffective in reducing tyrosinase activity during adult life when the melanocytes produce predominantly phaeomelanin. This suggests that different control mechanisms may operate in the hair follicular melanocytes during periods of eumelanin and phaeomelanin synthesis.

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Microheterogeneity of melanosome-bound tyrosinase from the Harding-Passey murine melanoma. Int J Biochem 19:227-234, 1987.
Abstract : The title study was directed towards the characterization of the origin of the microheterogeneity displayed by mammalian tyrosinase, the enzyme responsible for pigmentation in mammals. Tyrosinase was purified from the Harding Passey murin melanoma,

fractionated into a continuous series of subisozymic forms, and analyzed using various chem. and immunol. probes. Treatment with neuraminidase revealed that all the forms had similar amts. of sialic acid, and reactivity with various carbohydrate specific lectins showed that the isoenzymes also contained subterminal galactose, N-acetylglucosamine, and mannose, but lacked alpha-fucose. Amino acid compn. data indicated that the polypeptides of all the forms had identical residue contents. The sum of the evidence further supports the theory that the isoenzymic forms demonstrable for mammalian tyrosinase represent intermediate processing stages of the enzym from the nascent protein chain to the fully glycosylated, high mol. wt. form of tyrosinase that is localized within melanin granules.

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Inhibition of tyrosinase by coenzyme A. IRCS (Int Res Commun Syst) Med Sci 14:1217-1218, 1986.

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A study on the in vitro interactin between tyrosinase and glutathione S-transferase. Biochim Biophys Acta 913:386-394, 1987.
Abstract : The actions of glutathione S-transferase and tyrosinase on the in vitro prodn. of glutathionyl-3,4-dihydroxyphenylalanine and the dopachrome level in the presence of GSH and L-3,4-dihydroxyphenylalanine were studied. No clear evidence of complementarity between tyrosinase and glutathione S-transferase was obsd.; on the contrary, in the presence of glutathione S-transferase, the glutathionyl-3,4-dihydroxyphenylalanine yield was lower than with tyrosinase only, as measured by HPLC. The spontaneous conjugation of GSH with dopaquinone should probably be high enough to scavenge the toxic quinone and to produce precursors for phaemelanogenesis.

- Yoshimoto T, Yamamoto K, Tsuru D
Extracellular tyrosinase from Streptomyces sp. KY-453 : purification and some enzymatic properties. J Biochem 97:1747-1754, 1985.

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- Kurbanov Kh
Metabolic activity of melanosomes of skin and pigmented eye tissue. Izv Akad Nauk Turkm SSR, Ser Biol Nauk 73-75, 1987.

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- Sugita A, Tanaka T, Yoshioka H
Age-related changes of iris stromal melanocytes in human eyes. Jpn J Ophthalmol 30:174-179, 1986.
Abstract : Age-related changes of the melanocytes in the human iris stroma were studied by electron microscopy. The iris specimens were obtained during cataract surgery of patients aged from 70 to 84 years. The most characteristic age-related changes in the iris stromal melanocytes were formation of melanosome complexes in the cytoplasm. In addition, nuclear bodies were seen within the nucleus. The diameter of the nuclear bodies varied from 0.8 to 2.0 micron and they contained dense osmiophilic granules similar to melanin granules. Lipofuscin granules, which are known as an age-related marker of cardiac muscle cells and neurons, were not observed in the cytoplasm. The clinical significance of these age-related changes in the iris stromal melanocytes remains to be discussed in the future.

- Tsuchiya M, Hayasaka S, Mizuno K
Affinity of ocular acid-insoluble melanin for drugs in vitro. Invest Ophtalmol Visual Sci 28:822-825, 1987.
Abstract : The ability was examd. of drugs to bind with acid-insol. melanin obtained from various parts of bovine and swine eyes. Chloroquine, thioridazine, befunolol, pindolol, daunomycin, and 5-fluorouracil bound to melanin (pH 4.8, 7.4 and 8.0). Methotrexate bond to melanin (pH 4.8 but not at 7.4 and 8.0). Pilocarpine, epinephrine, acyclovir, vincristine and colchicine did not bind to ocular acid-insol. melanin.

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Distribution and properties of beta-adrenergic receptors in human iris-ciliary body. Invest Ophthalmol Vis Sci 28:420-430, 1987.

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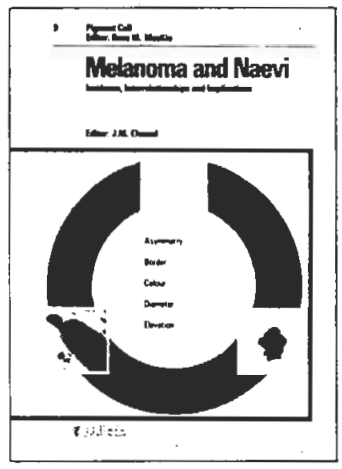

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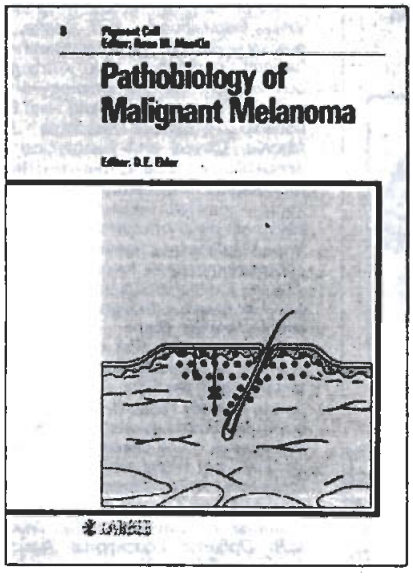

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